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TITLE: Preventing Blood Cancers and Other Malignancies in Military Personnel at Risk Due to Occupational Radiation Exposure

PRINCIPAL INVESTIGATOR: Stephen J. Kron

CONTRACTING ORGANIZATION: The University of Chicago, Chicago, IL

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Stephen J. Kron, Principal Investigator

E-Mail: skron@uchicago.edu

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The University of Chicago
5801 S. Ellis Avenue
Chicago, IL 60637

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14. ABSTRACT

We have initiated a project to examine the amino sugar N-acetylglucosamine, via its ability to increase protein O-GlcNAcylation, as a means to promote DNA double strand break repair and thereby prevent and mitigate the toxicity of radiation in the bone marrow, toward reducing both the acute and delayed effects, including malignancy. A major challenge has been adapting to limitations related to COVID-19 and then returning to full productivity. After delaying the initiation of research and adjusting our focus, *in vitro* research is well under way with *in vivo* studies continuing to lag. Nonetheless, work to date has set the stage for a productive second year of research.

15. SUBJECT TERMS
None listed.

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TABLE OF CONTENTS

	Page
1. Introduction	4
2. Keywords	4
3. Accomplishments	4
4. Impact	6
5. Changes/Problems	6
6. Products	6
7. Participants & Other Collaborating Organizations	6
8. Special Reporting Requirements (Award Chart)	21
9. Appendices	NA

1. Introduction

This project is directed at testing a non-toxic intervention as a means to protect individuals at risk of radiation exposures from damaging effects to the bone marrow and other proliferative tissues. Briefly, our work identified a core cellular metabolism pathway, the hexosamine biosynthetic pathway (HBP), as a determinant of radiation tolerance. The HBP incorporates metabolic inputs from glucose and glutamine to form UDP-GlcNAc. Then, O-GlcNAc transferase utilized the UDP-GlcNAc to transfer GlcNAc moieties to protein serines and threonines, leading to altered function, localization, stability and/or expression. Our data suggest that OGT substrates, including the EZH2 methyltransferase, are activated upon O-GlcNAcylation to enhance repair of DNA double strand breaks, promote cell survival, and/or resist cellular senescence after radiation exposure. The impetus for this project is that simply feeding cells the precursor amino sugar N-acetyl glucosamine (GlcNAc) is sufficient to drive the HBP and overall O-GlcNAcylation, leading to enhanced radiation tolerance *in vitro*. Feeding GlcNAc to animals or humans similarly increases O-GlcNAcylation, suggesting that this may be sufficient to enhance radiation tolerance *in vivo*. Our focus is on bone marrow and decreasing morbidity and mortality due to the acute hematopoietic syndrome and then late effects such as bone marrow failure and hematopoietic malignancies after accidental, occupational or military radiation exposures. Using bone marrow cultures and mouse models, we hope to explore if increasing O-GlcNAcylation via feeding with GlcNAc prior to and after otherwise lethal whole body irradiation may preserve hematopoiesis at the level of stem cell and precursor survival and proliferation.

Not surprisingly, beyond the expected difficulties of starting up a new project, we have faced unanticipated challenges this year. As a result of the pandemic and its impacts on our laboratories, the first year of this project has been far less productive than planned. Nonetheless, some progress has been made and the secon year of work is off to a promising start. As such, we anticipate being able to have a productive year and start catching up with the schedule for tasks and milestones.

2. Keywords

Radiation, bone marrow, metabolism, DNA repair, hematopoiesis, stem cells, precursors

3. Accomplishments

We have listed the tasks that were proposed in the SOW to be initiated and/or completed during the first 12 months and our progress on each:

Major Task 1: Establish bone marrow cultures

<u>Subtask 1: Isolate bone marrow with high culture viability.</u> We have established a simple workflow that allows us to culture bone marrow in the lab. Using a flow panel that detects hematopoietic stem and precursor cells (HSPC) to analyze the bone marrow, we detected 0.01-0.02% hematopoietic stem cells (HSCs) based on a marker pattern of CD150+, CD48-, Sca-1+, cKit+, Lin-. The stem cells displayed satisfactory viability upon isolation and then proliferated when grown in tissue culture.

<u>Subtask 2: Optimize culture growth and feeding.</u> Using mouse bone marrow cultures, we have examined culture conditions to obtain an optimal yield of HSCs. We started with Iscove Modified Dulbecco Media (IMDM) with stem cell factor (SCF) and interleukins 3 and 6 (IL3, IL6). Using the flow panel to detect HSPCs, the SCF+IL3+IL6 combination displayed the lowest proportion of HSCs compared to each factor used alone in IMDM. IMDM+SCF resulted in a sufficient proportion of HSCs and viable cells that it can be used for future cultures.

Major Task 2: Establish radiation response assays in cultures

<u>Subtask 1: Establish assays of DNA damage and senescence</u> We have made considerable progress in dissecting radiation response and its modulation by O-GlcNAcylation and related factors during the first year.

A highlight has been to develop a novel strategy to map γH2AX, a mark associated with DNA double strand break (DSB) detection and initiation of repair, across the genome over a time course following irradiation. Using K562 erythroleukemia cells as a model for bone marrow stem/progenitor cells and applying BLISS-seq to map DSBs across the genome and CUT&RUN to detect enrichment of γH2AX, we discovered that the initial distribution of γH2AX after irradiation is limited to transcriptionally active euchromatin. We found this is very likely linked to detection of DSBs being the limiting factor. In euchromatin, DSBs appear to be rapidly recognized via collisions with RNA polymerases. In turn, γH2AX appears considerably later in other domains such as repressed regions and heterochromatin, presumably via a mechanism where DSBs persist and then are detected only when replication forks collide with them. An important observation is that many DSBs are co-enriched with the H3 K27me3 mark, which is abundant in domains where γH2AX is delayed. As a result, many of these DSBs may not be repaired until they are recognized as damage during S phase, when they are likely to be detected via collision with a replication fork. Indeed, the H3 K27me3 enriched fraction of the genome does become decorated with γH2AX when assayed 24 h after irradiation, presumably once cells have reentered the cell cycle. This new view of DNA damage detection depending on chromatin mobilization during transcription or replication suggests novel mechanisms that may link epigenetic marks to DNA repair. As such, we are poised to apply this new tool to examining impacts of O-GlcNAcylation on DSB detection and repair across the genome.

In complementary work, we have continued to examine the mechanism by which O-GlcNAcylation enhances DSB repair. Although we are using cancer cell lines as a model, the fundamental mechanisms of DSB detection and repair appear to be quite similar in most proliferating human cells, albeit somewhat distinct in stem cells. This *in vitro* work has revealed that O-GlcNAcylation and poly-ADP ribose polymerase 1 (PARP1) appear to be acting in the same pathway. While this may be as simple as PARP1 being a substrate for O-GlcNAc transferase, our data may be more consistent with PARP1 and the relevant target(s) of OGT being distinct. GlcNac can compensate both for inhibition and knockdown of PARP1 to restore DSB repair. Consistent with this functional overlap, examining the cell cycle stage dependence of the O-GlcNAcylation effect on DSB repair also recapitulated the cell cycle dependence of PARP1 inhibition. DSB damage foci formation and resolution in G1 cells was more or less unaffected by OGT or PARP1 activity. All of the impact of modulating O-GlcNAcylation or PARylation appeared to be in S phase and likely G2.

Notably, DSB repair in G1 is limited to end-joining repair. Several mechanisms for rejoining a break can be utilized, but the dominant is conventional non-homologous end-joining (NHEJ), where the two ends are blunted off and then ligated. The presence of a sister chromatid in S phase and G2 permits some DSBs to be repaired by homologous recombination, but this requires activation of a 3'-5' DNA endonuclease to expose a short stretch of sequence to bind recombination proteins and allow homology search on the sister strand. Notably, though, even in S/G2, most breaks are repaired by NHEJ or other end-joining mechanisms, meaning the ends are generally protected from 3' resection. Toward mechanism, we examined the effect of O-GlcNAcylation on DSB repair at level of choice of repair mechanism between non-homologous end-joining (NHEJ) and homologous recombination (HR). In a striking finding using the Traffic Light reporter system, we observed that blocking OGT or PARP yielded a decrease in NHEJ repair and *increase* in HR. This pattern suggests an overall shunting of S/G2 repair away from end-joining and toward HR. We are now examining whether this reflects inappropriate 3' resection at breaks that would otherwise be repaired by NHEJ. We interpret the overall repair defect upon inhibition of O-GlcNAcylation to be linked to overloading HR by resecting too many breaks while increased O-GlcNAcylation may protect against resection to allow time for end-joining repair. A similar mechanism may underlie the role for PARP1 in DSB repair.

Notably, treatment with PARP inhibitors is associated with a high incidence of hematological toxicities. PARP1 activity can be enhanced, leading to increased DNA damage tolerance, by treating cells with its substrate NAD+ or the precursor nicotinamide dinucleotide (NMN) or nicotinamide riboside (NR). NMN or NR, like GlcNAc, are orally available, suggesting the value of treating with both agents to further increase repair capacity to improve bone marrow

Subtask 2: Determine effects of radiation using flow cytometry. We have established a flow cytometry-based assay to track DNA damage and repair by immunostaining with anti-γH2AX antibody and HSPC markers. We have initially validated this assay as a tool to examine the kinetics of recovery from DNA damage. We expect to be able to measure the impact of O-GlcNAcylation on resolution or persistence of γH2AX.

Subtask 3: Determine radiation effects on bone marrow cultures with single cell RNA-seq. Not initiated.

Major Task 3: Evaluate effects of increased O-GlcNAcylation on radiation response

Subtask 1: Develop methods to regulate O-GlcNAcylation in bone marrow culture. Not initiated.

Subtask 2: Evaluate effects of O-GlcNAcylation on bone marrow growth and differentiation. Not initiated.

Subtask 3: Confirm mechanisms of effects of increased O-GlcNAcylation on DSB repair, proliferation and senescence. Not initiated.

Major Task 4: Develop bone marrow irradiation model to examine impacts of O-GlcNAcylation

Subtask 1: Identify radiation dose producing <20% mortality within 2 weeks due to H-ARS. Not initiated.

Subtask 2: Obtain baseline data on H-ARS with respect to bone marrow function. Not initiated.

Subtask 3: Examine irradiation in Cux1 shRNA model. Not initiated.

Major Task 5: Examine impacts of O-GlcNAcylation on early bone marrow response

Subtask 1: Establish gavage treatment to increase bone marrow O-GlcNAc levels before and after irradiation. Not initiated.

Subtask 2: Examine effects of O-GlcNAcylation on blood counts after irradiation. Not initiated.

4. Impact

Nothing to report to date.

5. Changes/Problems

Project funding began as of July 1, 2020. While the University of Chicago had reopened sufficiently in early June, 2020 for research staff to be allowed to return to on-campus work, most members of the group continued to limit their hours in the lab until June, 2021. In turn, staffing and availability of animal facilities and other core resources critical for this project remained significantly constrained for the rest of 2020 and into early 2021. Although our laboratories had returned to close to normal function by the end of winter, considerable effort had to be devoted to trailing projects. Further, we had lost staff and were unable to fully replace them, let alone grow as planned. In response to these constraints, we did not begin spending on the project until October, 2020, shifted much of our focus to *in vitro* studies for the first year and strived to maintain a low burn rate overall. Although we otherwise controlled spending as much as feasible, salary and fringe costs were incurred from October, 2020 onward, so that a significant fraction of the first year budget was expended without the expected research outcomes being achieved.

We continue to face a challenge of not being able to fill the open postdoctoral researcher position with a qualified candidate. We are about to interview Sara Averbek, a Turkish national about to defend her doctoral dissertation at Technical University of Darmstadt, Germany. Ms Averbek is the first author on the highly relevant paper, "O-GlcNAcylation affects the pathway choice of DNA double-strand break repair", that recently appeared in *International Journal of Molecular Sciences*, https://doi.org/10.3390/ijms22115715 . If she were to join the lab and were interested in the PRCRP Impact project, she would be perfectly suited to pursue the *in vitro* studies.

6. Products

Nothing has been published as a result of this funding to date.

Three manuscripts on related topics that were initiated prior to this project but whose studies were partly supported by this funding are undergoing final edits and nearing submission. Authors partially or fully supported by this funding are underlined.

Global epigenetic analysis reveals H3K27 methylation as a mediator of double strand break repair
J. Lutze, D. Wolfgeher and S.J. Kron

Multi-dimensional epigenetic analysis reveals transcription as a primary driver of radiation-induced double strand break recognition
J. Lutze, J. Kurkewich, S. Khan, M.E. McNerney and S.J. Kron

Genomic studies controvert the existence of the CUX1 p75 isoform
M. Krishnan, M.D. Senagolage, J.T. Baeten, D.J. Wolfgeher, S.J. Kron and M.E. McNerney

and two more are close to having all data in hand and/or drafts written:

A direct double strand break tagging technique uncovers a role for SWI/SNF in rapid DNA damage repair
J. Lutze, D. Wolfgeher, B.T. Nicholson and S.J. Kron

O-GlcNAcylation promotes DNA repair in G2/M via a PARP-dependent pathway
E. Efimova, Y. Liu, and S.J. Kron

7. Participants & Other Collaborating Organizations

Name: Stephen Kron, MD-PhD
Project Role: PI
Research Identifier: 0000-0003-1518-2436
Person Month Worked: 2
Contribution to Project: Dr. Kron has been involved in planning and analysis of experiments and in coordinating activities of the research and technical staff.
Funding Support: See continuation pages.

Name: Megan McNerney, MD-PhD
Project Role: Co-Investigator
Research Identifier: 0000-0002-8260-3598
Person Month Worked: 0.5
Contribution to Project: Dr. McNerney has participated in developing the strategy to track DNA damage response across the genome.
Funding Support: See continuation pages.

Name: Sandeep Gurbuxani, MBBS-PhD
Project Role: Co-Investigator
Research Identifier: 0000-0003-0716-8730
Person Month Worked: 0.5
Contribution to Project: Dr. Gurbuxani has been available for consulation.
Funding Support: See continuation pages.

Name: Elena Efimova, PhD
Project Role: Senior research professional
Research Identifier: None
Person Month Worked: 9.0
Contribution to Project: Dr. Efimova has been studying the mechanism of modulation of DNA damage response and repair by O-GlcNAcylation *in vitro*.
Funding Support: Kron grants

Name: Julian Lutze, BS
Project Role: Graduate Student
Research Identifier: 0000-0002-8062-7756
Person Month Worked: 12
Contribution to Project: Mr. Lutze has focused on developing proteomic and genomic methods to measure how radiation-mediated damage is detected and repaired, using K562 as a model for bone marrow cells.
Funding Support: NA

Name: Joanna Pagacz, MA
Project Role: Technician
Research Identifier: None
Person Month Worked:12
Contribution to Project: Ms. Pagacz has been isolating bone marrow and participating in analysis of radiation effects.
Funding Support: NA

Name: DeShawn Thompson
Project Role: Technician
Research Identifier: None
Person Month Worked: 2
Contribution to Project: Mr. Thompson has been examining bone marrow proliferation and differentiation by flow cytometry.
Funding Support: NA

Other Support

Kron, Stephen

PREVIOUS:

Title: *Radiation response within the tumor microenvironment*
Supporting Agency: NIH/NCI, R01 CA164492
Project Goals: Examining determinants of radiation resistance and response mediated by both cancer and host tissue.
Specific Aims:
Aim 1. Image and model DSB kinetics after irradiation in relation to the microvascular tracking hypoxia and metabolism as potential determinants of repair
Aim 2. Examine the senescence response after irradiation in relation to the microenvironment
Aim 3. Examine angiogenesis and tumor regrowth after radiation in relation to tumor metabolism, hypoxia and senescence
Period of Performance: 9/21/11-7/31/17
Level of Effort: 32%; 3.8 CME
Contact: Debra Sowell
Debra.sowell@nih.gov
Overlap: None

Title: *PARP inhibition to enhance induction for head and neck cancer*
Supporting Agency: NIH/NCI, R01 CA176843
Project Goals: Examine PARP inhibitor veliparib as an immunogenic sensitizer for induction therapy.
Specific Aims:
Aim 1: Examine the interactions of veliparib with docetaxel, cisplatin and/or 5-fluorouracil in vitro and in xenograft and syngeneic tumors.
Aim 2: Pursue A) Proteomic analysis of the cell surface proteome and SASP and B) Gene expression analysis of signaling pathways to define the differential response of HNSCC cell lines to TPF plus or minus veliparib.
Aim 3: Characterize patient biopsy material in light of the molecular analyses performed with model systems.
Period of Performance: 9/1/13-8/30/17
Level of Effort: 10%, 1.2 CME
Contact: Mary Wolpert PhD
wolpertm@mail.nih.gov
Overlap: None

Title: *Environmentally-adaptive nanoparticles with focal irradiation for cancer therapy*
Supporting Agency: NIH/NIBIB, R01 EB017791 (Y. Yeo Purdue U., PI)
Project Goals: Studies directed at targeting novel nanoparticles to tumors.
Specific Aims:
Aim 1. To optimize synthesis of ENPs loaded with paclitaxel (PTX).
Aim 2. To optimize and validate IGRIP for delivery of NPs to prostate cancer tumors in mice.
Aim 3. To determine biodistribution and anti-tumor activity of PTX/ENPs.
Performance Period: 3/1/14-2/28/18
Level of Effort: 9%, 1.0 CME
Contact: Yoon Yeo PhD
yyeo@purdue.edu
Overlap: None

Title: *Probing the immune microenvironment to distinguish indolent from aggressive prostate cancer*
Supporting Agency: NIH/NCI/Chicago Prostate SPORE P50 CA180995 Pilot
Project Goals: Multiplex microscopy method to interrogate tumor immune microenvironment
Specific Aims:
Aim 1 Validate four-plex panels that interrogate the PCa immune microenvironment on individual FFPE blocks and tissue microarrays

Aim 2 Apply multiparameter imaging cytometry to A) Collect multiplex IF data on a training set of PCa biopsy TMAs and B) Identify candidate immune microenvironment biomarkers associated with indolence vs. aggressive behavior.
Aim 3 Evaluate candidate biomarkers on a test set of PCa biopsy TMAs and confirm feasibility with individual clinical samples.
Performance Period: 8/1/16-7/1/18
Level of Effort: 2%, 0.2 CME
Contact: Robyn Egan
regan@bsd.uchicago.edu
Role: Co-PI
Overlap: None

Title: *Radiation-enhanced delivery of checkpoint blockade antibodies*
Supporting Agency: Cancer Research Institute, CLIP Award
Project Goals: Targeted radiation-mediated delivery of antibodies for immunotherapy
Specific Aims:
Aim 1: Validate radiation-enhanced permeability and retention as a tool for targeted delivery of immunological checkpoint inhibitor antibodies to murine melanoma tumors.
Aim 2: Examine significance of enhanced delivery and tumor penetration on synergy of immune checkpoint inhibitor antibodies with image-guided radiation.
Performance Period: 7/1/17-6/30/19
Level of Effort: 10%, 1.2 CME
Role: PI
Contact: Ryan Godfrey
rgodfrey@cancerresearch.org
Overlap: None

Title: *Image-guided radiation-induced permeability (IGRIP) for IGDD*
Supporting Agency: NIH/NCI, R01 CA199663
Project Goals: We intend to leverage image-guided radiation as a means to target nanomedicines to tumors.
Specific Aims:
Aim 1. Optimize and validate image-guided radiation-induced permeability (IGRIP) and establish IGRIP for image-guided drug delivery (IGDD) to prostate cancer tumors in mice
Aim 2. Towards establishing radiation-guided gene delivery, develop novel nucleic acid vectors for systemic injection and validate these nanocarriers by demonstrating efficient radiofection of mouse PCa tumor models with reporter genes
Aim 3. Toward translation of radiation-guided gene therapy, a) apply mouse models of PCa to demonstrate image-guided radiofection of CD-UPRT, evaluate CD-UPRT/5-FC enzyme prodrug therapy and examine synergy with radiation and b) target oncogenes by radiofection of siRNA for knockdowns and CRISPR for knock outs.
Performance Period: 7/1/15-6/30/2021
Level of Effort: 13%, 1.5 CME
Role: MPI with R. Weichselbaum
Contact: Pushpa Tandon
Tandonp@mail.nih.gov
Overlap: None

Title: *Nanoscale metal-organic frameworks for light triggered and X-ray induced photodynamic therapy of head and neck cancers*
Supporting Agency:NIH/NCI, U01 CA198989 (W. Lin, R. Weichselbaum MPIs)
Project Goals: Radiation-activated nanoparticle cancer therapy technology
Specific Aims:
Aim 1: Synthesis and characterization of nanoscale metal-organic frameworks (NMOFs) for NIR triggered and X-ray induced PDT.
Aim 2: Evaluation of NIR triggered PDT efficacy in experimental head and neck cancers.
Aim 3: Evaluation of X-ray induced PDT efficacy in experimental head and neck cancers.

Performance Period: 9/1/15-8/31/20
Level of Effort: 9%, 1.0 CME
Role: Co-I
Contact: Wenbin Lin PhD
wenbinlin@uchicago.edu
Overlap: None

Title: *Probing impact of cellular senescence on intestinal crypt function using organoid models*
Pilot & Feasibility grant; NIH, UChicago DDRCC Pilot
Project Goals: Examining aging in intestinal organoids using single cell methods.
Specific Aims:
Aim 1: Establish organoid formation defects associated with cellular senescence from models of intestinal epithelial aging including naturally aged mice, irradiated mice and mice lacking telomerase.
Aim 2: Examine effects of eliminating senescent cells on rescuing organoid formation by depleting senescent cells using genetic or chemical ablation.
Aim 3: Evaluate effects of genetic or chemical ablation of senescent cells on intestinal epithelial aging in vivo.
Period of Performance: 12/1/19-11/30/20
Level of Effort: 2%, 0.2 CME
Role: PI
Contact: Kailee Zingler
kzingler@bsd.uchicago.edu
Overlap: None

Title: *Tag-ChIP-MS for analysis of chromatin-level regulation of DNA repair*
Supporting Agency: NIH/NCI, R21 CA213247
Project Goals: We will leverage advanced tools for genome editing, protein tagging, chromatin enrichment and LC-MS/MS analysis to establish a new approach to chromatin proteomics
Specific Aims:
Aim 1. Establish split MPLUM tagging to visualize proteins involved in IRIF formation and resolution
Aim 2. Leverage split MPLUM tagging for TAG-CHIP-MS to dissect chromatin dynamics at IRF
Performance Period: 3/1/17-2/29/20 (NCE 2/28/21)
Level of Effort: 2%, 0.2 CME
Role: PI
Contact: John Knowlton
Jk339o@nih.gov
Overlap: None

Title: *Targeting Cancer Metabolism as a Novel Synthetic Lethality Strategy For BRCA Deficient Breast Cancers*
Funding Agency: NIH/NCI, F32 CA250347
Project Goals: NRSA to Tamica Collins PhD, a post-doctoral fellow in the Kron laboratory.
Specific Aims:
Aim 1. Assess effects of modulating O-GlcNAcylation in BRCA breast cancer in vitro and in vivo
Aim 2. Evaluate OGT inhibitors as PARPi sensitizers in BRCA breast cancer in vitro and in vivo
Aim 3. Define gene expression signatures for activation of O-GlcNAcylation in BRCA breast cancer
Period of Performance: 6/1/20-5/31/22 (Early Termination)
Level of effort: 0
Role: Mentor and Sponsor
Contact: Sonia B. Jakowlew PhD
jakowles@mail.nih.gov
Overlap: None

ACTIVE:

Title: *Veliparib interactions with genotoxic and immuno-therapy: Therapy-induced senescence and anti-tumor immunity*

Supporting Agency: AbbVie/UChicago collaboration grant
Project Goals: Exploring determinants of response to PARP inhibition including potentiating immunotherapy
Specific Aims:
Aim 1 Examine responses to Veliparib combined with a platinum agent or radiation in NSCLC PDX models in immunodeficient NSG mice.
Aim 2(A) Examine responses to Veliparib combined with genotoxic agents in NSCLC PDX models in CD34+ HSC humanized NSG mice and (B) Examine responses to Veliparib combined with genotoxic agents in i) CT26 tumor spheroids co-cultured with BALB/c mouse splenocytes and in ii) CT26 and 4T1 tumors in immunocompetent BALB/c mice.
Aim 3 Examine potentiation of Veliparib effects by PD-1/PD-L1 immune checkpoint blockade in i) CT26 tumor spheroids co-cultured with BALB/c mouse splenocytes and in ii) CT26 and 4T1 tumors in immunocompetent BALB/c mice.
Performance Period: 10/1/16-12/31/21
Level of Effort: 9%, 1.0 CME
Role: PI
Contact: Eric Johnson
Eric.f.johnson@abbvie.com
Overlap: None

Title: *Single cell analysis of tumor immune infiltrates to track breast cancer immunotherapy*
Supporting Agency: NCI, UCCCC Pilot
Project Goals: Evaluate scRNA-seq analysis of the immune repertoire and apply this approach to documenting response to immune checkpoint blockade.
Specific Aims:
Aim 1 Modeling anti-PD-1/PD-L1 checkpoint blockade in mouse models of breast cancer to develop and validate scRNA-seq as an assay for anti-tumor immune activation
Aim 2 Applying scRNA-seq to analysis of on-treatment biopsies from breast cancer patients receiving anti-PD-1/PD-L1 therapy
Performance Period 12/1/17-11/30/18 (NCE 11/30/21)
Level of Effort: 2%, 0.2 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

Title: *Probing breast cancer immune infiltrates to monitor checkpoint blockade response*
Funding Agency: NCI, UCCCC Pilot
Project Goals: T3 and single cell analysis of TNBC biopsies to track response to immune checkpoint blockade.
Specific Aims:
Aim 1. Apply single cell RNA sequencing to discover biomarkers of response to immune checkpoint blockade (ICB) antibody therapy.
Aim 2. Establish workflow that applies T3 for rapid and reproducible 3D analysis in core needle biopsies from TNBC patients.
Aim 3. Validate candidate biomarkers of response to ICB therapy using T3 for analysis of TNBC core needle biopsy tissue
Period of Performance: 2/2/20-8/31/21
Level of effort: 2%, 0.2 CME
Role: PI
Contact: Toni Cipriano-Steffens
tciprian@medicine.bsd.uchicago.edu
Overlap: None

Title: *Leveraging DNA repair to enhance CRISPR genome editing*
Funding Agency: Chicago Biomedical Consortium, Catalyst Award
Project Goals: Examining novel strategy to increase HDR by CRISPR for site-directed mutagenesis based on recruiting DNA repair activities.

Specific Aims:
Aim 1: Examine the ability of DNA repair enzymes linked to resolution of DNA-protein crosslinks to detect and resolve stable Cas9-DSB complexes in vitro.
Aim 2: Evaluate the efficiency of Cas9-mediated homology-directed repair using donor DNAs that incorporate specific forms of DNA damage (DNA-repair beacons) to target DNA repair to the Cas9-DSB complex
Period of Performance: 3/1/19-2/28/22 (NCE)
Level of effort: 2%, 0.2 CME
Role: MPI with L. Hanakahi, UIC
Contact: Karen R. Snapp, DDS, PhD
ksnapp@northwestern.edu
Overlap: None

Title: *Mechanisms determining local and systemic anti-tumor immune response after metastasis-directed image-guided radiation combined with PD-1/PD-L1 checkpoint blockade*
Funding Agency: METAVivor, Research Award
Project Goals: Mouse model studies of radiation to potentiate immune checkpoint blockade in breast cancer.
Specific Aims:
Aim 1. Validate radiation-targeted delivery of anti-PD-L1 to both primary and metastatic murine mammary tumors.
Aim 2. Examine determinants of synergy of anti-PD-L1 with radiation
Aim 3. Explore requirements fo systemic anti-tumor immune response targeting distant metastases
Period of Performance: 2/1/20-1/31/22
Level of Effort: 9%, 1 CME
Role: PI
Contact: Sonya Negley
Sonya@metavivor.org
Overlap: None

Title: *Targets of Reactive Lipid Species regulating DNA damage response and cell senescence*
Supporting Agency: NIH/NCI, R01 CA217182
Project Goals: To establish a new mechanism of action for etoposide and related chemotherapy agents
Specific Aims:
Aim 1A) Examine the effects of lipid peroxidation and reactive lipid species on Top2 poisoning and cell senescence, and B) Examine modification of Top2 by 4-HNE and other reactive lipid species and mutate reactive sites to examine functional significance.
Aim 2 Directly test whether DNA damage is sufficient to induce accelerated senescence and examine if 4-HNE and DNA damage interact additively (same pathway) or synergistically (distinct pathways).
Aim 3A) Apply proteomics to identify targets of RLS in etoposide-treated cells, and B) Examine Top2 as a signal transducer mediating the adaptive response to oxidative stress and ionizing radiation.
Performance Period: 7/1/17-6/30/22
Level of Effort: 15%, 1.8 CME
Role: PI
Contact: Paul Okano PhD
Po8k@nih.gov
Overlap: None

Title: *Chemotherapy delivery with nanoparticles for targeted induction of immunogenic cell death*
Funding Agency: NIH/NCI, R01 CA232419 (Y. Yeo Purdue, PI)
Project Goals: Studies are directed at targeting nanoparticles bearing immune checkpoint antagonists to tumors.
Specific Aims:
Aim 1. To develop ICD-inducing NPs and evaluate their ability to promote an anti-tumor immune response.
Aim 2. To evaluate the anti-cancer effect of ICD-inducing NPs in combination with local ionizing radiation.
Aim 3. To investigate the contribution of ICD-inducing NPs to ICB therapy.
Period of Performance: 4/1/18-3/31/23
Level of effort: 9%, 1.0 CME

Role: Co-Investigator
Contact: Yoon Yeo PhD
yyeo@purdue.edu
Overlap: None

*Title: *Systemic delivery of short nucleic acid by anionic flexible carriers for cancer immunogene therapy*
Funding Agency: NIH (Yoon Yeo, Purdue)
Project Goals: *Studies of a soft nanocapsule as a gene carrier.*
Specific Aims:
Aim 1. To optimize design and production of Nanosac for multigene targeting
Aim 2. To define toxicity, pharmacokinetics (PK), biodistribution (BD), and pharmacodynamics of Nanosac
Aim 3. To leverage systemic delivery of Nanosac and tumor targeting by image-guided radiation
Period of Performance: 04/2021-03/2025
Level of effort: 15%; 1.80 CME
Role: Y. Yeo (PI), S. Kron (MPI)
Contact: Yoon Yeo PhD
yyeo@purdue.edu
Overlap: None

Title: *Bioinspired chemical probe approach targeting telomerase reverse transcriptase*
Funding Agency: NIH/NCI R01 CA254047
Project Goals: Subcontract for biological studies to further develop covalent TERT inhibitors to probe telomere and non-canonical roles of TERT.
Specific Aims:
Aim 1. Advance chrolactomycin analogs to inhibit htert in cells.
Aim 2. Explore selectivity and define extra-telomeric roles for htert catalytic activity with chrologs.
Aim 3. Investigate effects of chrologs on radiation sensitivity, tumor formation, recurrence and metastasis in the CT26 mouse colon carcinoma model.
Period of Performance: 7/1/20-6/30/25
Level of Effort: 9%, 1 CME
Role: MPI
Contact: Sharad Verma PhD
sharad.verma@nih.gov
Overlap: None

Title: *Lipid signaling in cellular senescence and tissue aging*
Funding Agency: NIH/NIA R01 AG069865
Project Goals: Study to examine role for lipid peroxidation and accelerated senescence in pulmonary fibrosis.
Specific Aims:
Aim 1. Characterize the lipidomic changes in pulmonary cell senescence in vitro and in vivo
Aim 2. Examine impacts of modulating sphingolipid, ceramide and other lipid pathways on senescence
Aim 3. Target lipid metabolism to block senescence and delay pulmonary fibrosis
Period of Performance: 9/1/20-8/31/25
Level of Effort: 9%, 1 CME
Role: PI
Contacts: Yih-Woei Fridell PhD
Yih-Woei.fridell@nih.gov
Overlap: None

Title: *Nanoscale Metal-Organic Frameworks Enable Radiotherapy-Radiodynamic Therapy and Deliver CpG Oligodeoxynucleotides to Generate Tumor Vaccines and Potentiate Immunotherapy of Head and Neck Cancers*
Funding Agency: NIH/NCI
Project Goals: This project examines cancer therapy with MOFs as nanomedicines for immunotherapy.
Specific Aims:
Aim 1: Elucidate the cellular mechanisms of nMOF-mediated RT-RDT and CpG oligonucleotides.

Aim 2: Profile tumor microenvironment and extracellular matrix after treatment with RT-RDT.
Aim 3: Investigate the anticancer efficacy and adaptive immune response of nMOF/CpGmediated RT-RDT and immunotherapy
Aim 4: Determine novel immunotherapy combinations that are potentiated by RT-RDT in HNSCC models resistant to PD-1/PD-L1 blockade.
Period of Performance: 7/1/20-6/30/25
Level of Effort: 5%, 0.60 CME
Role: Co-Investigator
Contact: Jennifer Couch PhD
couchj@mail.nih.gov
Overlap: None

Title: *Enabling T3 imaging cytometry of the tumor immune microenvironment in formalin fixed paraffin embedded (FFPE) biopsy tissue*
Funding Agency: Duckworth Foundation; (University of Chicago Cancer Center)
Project Goals: Studies to accelerate translation of 3D imaging to its potential commercial applications.
Specific Aims:
Aim 1: Adapt T3 to enable 3D imaging cytometry in FFPE, using 20-50 µm thick macrosections cut from archival head and neck cancer tissue samples to examine immune microenvironment.
Aim 2: Validate 3D cytometry in FFPE macrosections by comparing T3 analysis of immune microenvironment on fresh tissue and fixed and embedded thick sections from individual head and neck cancers.
Aim 3: Demonstrate higher sensitivity, specificity and quantitative resolution of T3 3D cytometry in FFPE thick sections over conventional multiplex IHC in thin sections.
Performance Period: 5/2021 – 4/2022 (NCE)
Level of Effort: 2% 0.24 CME
Role: PI
Contact: Robyn Egan
regan@bsd.uchicago.edu
Overlap: None

PENDING:

Title: *Genome instability driven by transcription and DNA replication conflict in lung cancers in never smokers*
Funding Agency: American Cancer Society
Project Goals: Examine genomic instability patterns in cancer genomes for signatures.
Specific Aims:
Aim 1. Identify complex rearrangements driven by transcription-replication collision in LCINS.
Aim 2. Identify simple rearrangements driven by transcription-replication collision in LCINS.
Performance Period: 1/2022-12/2025
Level of Effort: 0.24 CME
Role: Co-I
Contact: Lixing Yang, The University of Chicago
lixingyang@uchicago.edu
Overlap: None

Title: *ChicAgo Center for Health and EnvironmenT (CACHET)*
Funding Agency: NIH/NIEHS P30 ES027792
Project Goals: CACHET will continue to promote multidisciplinary environmental health research among clinician, laboratory and population scientists from two Chicago area universities with complementary strengths and structure to understand, evaluate and ultimately reduce environmental health related disparities among residents of the region and beyond.
Specific Aims:

Performance Period: 4/22-3/27
Level of Effort: 0.36 CME
Role: Co-I

Contact: H. Ahsan, The University of Chicago
habib@uchicago.edu
Overlap: None

Title: *Bioinspired chemical probe approach targeting telomerase reverse transcriptase (Revision/Supplement)*
Funding Agency: NIH/NCI R01 CA254047-S1
Project Goals: Subcontract to add new objectives to evaluate TERT inhibitors to target therapy resistance in cancer
Specific Aims:
Aim 1. Advance chrolactomycin analogs to inhibit hTERT in cells.
Aim 2. Explore selectivity and define extra-telomeric roles for hTERT catalytic activity with chrologs.
Aim 3. Investigate effects of chrologs on radiation sensitivity, tumor formation, recurrence and metastasis in the CT26 mouse colon carcinoma model.
Performance Period: 06/22-05/25
Level of Effort: 2%; 0.24 CME
Role: MPI
Contact: Sharad Verma PhD
sharad.verma@nih.gov
Overlap: None

Title: *Protein enrichment technology for secreted proteome tissue mapping*
Funding Agency: NIH/NCI; University of MN
Project Goals: Develop new method to capture secreted proteins.
Specific Aims:
Aim 1. Develop magnetic bead-tethered peptide libraries for generic affinity proteomics by dynamic range compression.
Aim 2. Develop approaches to employ bead-tethered libraries for tissue mapping.
Performance Period: 3/22-2/25
Level of Effort: 2%; 0.24 CME
Role: Co-I
Contact: L. Parker
llparker@umn.edu
Overlap: None

Title: *Reactive lipid species adductome linking oxidative stress, cellular senescence and lung cancer risk*
Funding Agency: NIH/NCI
Project Goals: Survey the targets of lipid aldehydes induced by oxidative stress in lung cells using proteomics.
Specific Aims:
Aim 1 Characterize the RLS adductome associated with oxidative stress
Aim 2 Determine the RLS adductome in senescent mouse pulmonary fibroblasts and aged lungs
Aim 3 Examine topoisomerase-DNA cleaved complexes and other DNA-protein complexes (DPCs) toward identifying biomarkers of RLS-mediated genomic stress
Performance Period: 3/22-2/27
Level of Effort: 15%, 1.8 CME
Role: PI
Contact: NIH CSR
PO to be determined
Overlap: None

Megan McNerney

PREVIOUS

- Title: **Determining the role of CUX1 in myeloid neoplasia (McNerney)**
- Agency: NIH/NCI - 5K08CA181254-05
- Project Goals: The overall objective of the current application is to identify these biological functions and the molecular pathways regulated by CUX1, and how CUX1 haploinsufficiency alters these programs.
- Specific Aims: Aim 1: Identify the aberrant CUX1 transcription targets in acute myeloid leukemia. Aim 2: Identify the mechanisms of human CUX1 tumor suppressor activity.
- Performance Period: 9/16/14 - 8/31/19
- Effort: 50%
- Contracting/Grants Officer: Susan E Lim
    - o Contact Information: Email: lims@mail.nih.gov Phone:

Overlap with the Proposed Project: None

- Title: **Synergistic Role of the Microenvironment and MDS Stem Cells: A Model for the Pathogenesis and Treatment of MDS (LeBeau)**
- Agency: Edward P. Evans Foundation
- Project Goals: The overarching goal of our project is to integrate studies of the marrow microenvironment and hematopoietic stem cells (HSCs) to examine the novel hypothesis that deregulation of WNT signaling in the stroma is an early event that leads to the acquisition of mutations in HSCs, leading to myelodysplastic syndrome, and that mitigation of WNT signaling is a viable therapeutic target.
- Specific Aims: 1. To identify the molecular targets of altered WNT signaling in MSCs and HSCs derived from our MDS mouse model, and from MDS patients, particularly those with a del(5q); and 2. To extend our studies evaluating whether the microenvironment is a viable target in MDS for treatment or prevention of progression, and whether inhibition of aberrant WNT signaling in the niche in combination with standard or investigational therapy is a viable therapeutic approach using humanized mouse models, and by extending studies of our mouse models.
- Performance Period: 9/1/17 – 8/31/19
- Effort: 0.60 CM (5%)
- Contracting/Grants Officer: Michael Lewis, Ph.D.
    - o Contact Information Email: grants@epefoundation.org

Overlap with the Proposed Project: None

- Title: **Establishing a genetically accurate preclinical model of high-risk myeloid malignancy (McNerney)**
- Agency: The Brinson Foundation
- Project Goals: The overall objective of the project funded by the Brinson Foundation is to determine the combined impact of Cux1 insufficiency and oncogenic Ras in cancer development.
- Specific Aims: Aims of Year 1 of the project were to: 1) determine the malignant myeloid phenotype in shCux1 x NrasG12D mice, and 2) identify the molecular mechanism(s) by which combinatorial loss drives disease. The specific Aims for Year 2 of this proposal are to 1) determine the role for oncogenic Nras and Cux1 knockdown in myeloid transformation through increased hematopoietic

stem cell survival and self- renewal; and 2) inhibit a pathway induced in Cux1lowxNrasG12D mice, such as PI3K, to block the malignant phenotype.

- Performance Period: 12/1/17 – 11/30/19
- Effort: .24 CM (2%)
- Contracting/Grants Officer: Jamie B. Bender
  - Contact Information: Email: Jamie.bender@brinsonfoundaiton.org Phone:

Overlap with the Proposed Project: None

- Title: **Molecular mechanisms of myeloid suppressor genes on chromosome 5 (LeBeau)**
- Agency: NIH/NCI - R01 CA190372-05
- Project Goals: The overall goal of this project is to identify cooperating mutations and genetic pathways leading to alkylating agent-induced t-MN with a del(5q).
- Specific Aims: Aim 1. To identify the molecular mechanisms of transformation by EGR1 by: a. Identifying the transcriptional targets of, and cellular pathways regulated by, EGR1 in normal hematopoietic stem cells (HSCs), and t-MNs with a del(5q); b. Examining the mechanism by which cell intrinsic loss of Egr1 and Apc cooperate with Tp53 loss in a mouse model of t-MN; and c. Examining the relationship of transcriptional regulatory pathways of the CUX1 transcription factor (a myeloid TSG on 7q22.1) and EGR1, and the mechanism by which lesions on 5q and 7q cooperate. Aim 2. To identify genetic mutations that cooperate with haploinsufficiency of EGR1 and/or APC in the pathogenesis of myeloid neoplasms by: a. Characterizing the genomic pattern of myeloid leukemias arising in mice with haploinsufficiency for Egr1, Apc, and Tp53; b. Expanding upon our studies showing that Egr1 haploinsufficiency cooperates with mutations induced by alkylating agents (ENU) to induce myeloid neoplasms by conducting genomic analysis of myeloid neoplasms arising in ENU-treated Egr1+/- mice; and c. Evaluating the cooperative role of candidate myeloid suppressor genes on 5q, e.g., CSNK1A1 (5q32, plays a critical role in hematopoiesis), SPRY4 (5q31.3, shown by S. Lowe to cooperate with Tp53 loss to promote AML), and a lysine-specific demethylase gene, KDM3B (5q31.2
- Performance Period: 2/1/15 - 1/31/20
- Effort: 0.36 CM (3%)
- Contracting/Grants Officer: Ian M Fingerman
  - Contact Information: Email: fingerma@mail.nih.gov Phone:

Overlap with the Proposed Project: None

- Title: **The role of CUX1 in human myelopoiesis (McNerney)**
- Agency: American Society of Hematology
- Project Goals: The objective of this proposal is to identify the role for CUX1 in human HSCs and the molecular pathways downstream of CUX1 haploinsufficiency that lead to malignant hematopoiesis.
- Specific Aims: Aim 1: Hypothesis —CUX1 transcriptionally regulates proliferation and differentiation genes in HSPCs. This will be tested by innovative functional genomic analyses including differential chromatin accessibility and gene expression due to CUX1 haploinsufficiency. Aim 2: Hypothesis — CUX1 suppresses human HSPC proliferation, blocks myelomonocytic differentiation, and is required for megakaryocyte and erythroid differentiation. This hypothesis will be tested by assays including cell-cycle, self-renewal, and myeloid/erythroid differentiation of cord-blood derived human HSCs with and without CUX1 haploinsufficiency.
- Performance Period: 7/1/18 – 6/30/20
- Effort: 0.6 CM (5%)
- Contracting/Grants Officer: Patricia Frustace
  - Contact Information: Email: awards@hematology.org Phone:

Overlap with the Proposed Project: None

- Title: **Tag-ChIP-MS for analysis of chromatin-level regulation of DNA repair (Kron)**
- Agency: NIH/NCI - R21CA213247-03
- Project Goals: The aim of this project is to establish Tag-ChIP-MS as an innovative technology for imaging-and-capture tagging to advance analysis of chromatin dynamics by microscopy and proteomics.
- Specific Aims: Aim 1. Establish split MPLUM tagging to visualize proteins involved in IRIF formation and resolution, Aim 2. Leverage split MPLUM tagging for TAG-CHIP-MS to dissect chromatin dynamics at IRF
- Performance Period: 3/1/17-2/29/21
- Effort: 0.24 CM (2%)
- Contracting/Grants Officer: John R Knowlton
    - Contact Information: Email: jk339o@nih.gov Phone:

Overlap with the Proposed Project: None

CURRENT

- Title: **Regulation of hematopoiesis by CUX1 (McNerney)**
- Agency: NIH/NCI - 1R01HL142782-02
- Project Goals: The overall objective is to determine the transcriptional role for CUX1 in normal HSPCs and erythroid progenitors and the pathways downstream of CUX1 haploinsufficiency that block erythroid differentiation.
- Specific Aims: Aim 1: Overall hypothesis – CUX1 is a transcriptional regulator of HSPC homeostasis conserved in mice and humans. Aim 2: Overall hypothesis – CUX1 promotes erythroblast cell cycle exit necessary for terminal differentiation by suppressing PI3K signaling.
- Performance Period: 7/15/18 – 6/30/23
- Effort: 1.38 CM (11.5%)
- Contracting/Grants Officer: C Brian Bai
    - Contact Information: Email: brian.bai@nih.gov Phone:

Overlap with the Proposed Project: None

- Title: **The impact of chromosome 7q deletions in juvenile mylelomonocytic leukemia (McNerney)**
- Agency: NIH/NCI - R01 CA231880-02
- Project Goals: The long-term goal of this proposal is to understand the molecular pathogenesis of -7/ del(7q) and to reveal new therapeutic targets for JMML patients.
- Specific Aims: Aim 1: Identify the cellular and molecular mechanisms by which Cux1 knockdown and Ras cooperate in JMML. Aim 2: Define the pathogenesis of combinatorial dosage imbalance of 7q genes in JMML.
- Performance Period: 9/20/18-8/31/2023
- Effort: 1.38 CM (11.5%)
- Contracting/Grants Officer: Chamelli Jhappan
    - Contact Information: Email: jhappanc@mail.nih.gov Phone:

Overlap with the Proposed Project: None

- Title: **The genetic and environmental etiology of therapy-related myeloid neoplasms (McNerney)**
- Agency: American Cancer Society - #132457-RSG-18-171-01-LIB
- Project Goals: The overall objective of the current application is to identify the mechanism by which CUX1 deficiency drives t-MN.
- Specific Aims: Aim 1: Hypothesis – PI3K inhibition blocks the genetic interaction of CUX1-loss and RAS signaling in myeloid transformation. Aim 2: Hypothesis – Insufficient CUX1 causes increased HSC 'fitness' in response chemotherapy due to increased PI3K activity leading to clonal expansion and t-MN.
- Performance Period: 01/01/19 - 12/31/22
- Effort: 0.6 CM (5%)
- Contracting/Grants Officer: Janet Meadows-Harriss
    - Contact Information: Email: janet.harris@cancer.org; Phone:

Overlap with the Proposed Project: None

Title: *Cancer Center Support Grant - Molecular Mechanisms of Cancer Core*
Supporting Agency: NIH/NCI 4P30CA014599-46 (PI: Odunsi)
Contracting/Grants Officer Contact: David G Ransom

david.ransom@nih.gov
Performance period: 5/22/18 - 3/31/23
Level of Funding:
Time Commitments: 0.6 CM, (5%)
Brief Description: The overall goal of the University of Chicago Medicine Comprehensive Cancer Center is to discover and translate new cancer-specific knowledge to prevent, detect, and treat cancer.
Overlap with the Proposed Project: None

SUBMITTED/PENDING

Title: Genomic interrogation of high-risk myeloid neoplasms to identify new therapies
Supporting Agency: Leukemia & Lymphoma Society
Contracting/Grants Officer Contact: researchprograms@lls.org
Performance period: 10/1/21 – 9/30/26
Level of Funding:
Time Commitments: 4.99 CM (41.59%)
Brief Description: Over 50,000 people are diagnosed with a myeloid neoplasm every year in the U.S. alone. A high-risk subset of patients is unresponsive to treatment and their survival is less than a year. The long-term goal of my lab is to improve the outcome for these patients. To this end, our research focuses on understanding the underlying genomic abnormalities in high-risk myeloid neoplasms, to identify new treatment avenues.
Overlap with the Proposed Project: None

Sandeep Gurbuxani

Previous, Current, and Pending Support

PREVIOUS
None

CURRENT
- Title: **Regulation of hematopoiesis by CUX1 (McNerney)**
- Agency: NIH/NCI - 1R01HL142782-02
- Project Goals: The overall objective is to determine the transcriptional role for CUX1 in normal HSPCs and erythroid progenitors and the pathways downstream of CUX1 haploinsufficiency that block erythroid differentiation.
- Specific Aims: Aim 1: Overall hypothesis – CUX1 is a transcriptional regulator of HSPC homeostasis conserved in mice and humans. Aim 2: Overall hypothesis – CUX1 promotes erythroblast cell cycle exit necessary for terminal differentiation by suppressing PI3K signaling.
- Performance Period: 7/15/18 – 6/30/23
- Effort: 0.24 CM (2%)
- Contracting/Grants Officer: C Brian Bai
    - Contact Information: Email: brian.bai@nih.gov Phone:

Overlap with the Proposed Project: None

- Title: **The impact of chromosome 7q deletions in juvenile mylelomonocytic leukemia (McNerney)**
- Agency: NIH/NCI - R01 CA231880-02
- Project Goals: The long-term goal of this proposal is to understand the molecular pathogenesis of -7/del(7q) and to reveal new therapeutic targets for JMML patients.
- Specific Aims: Aim 1: Identify the cellular and molecular mechanisms by which Cux1 knockdown and Ras cooperate in JMML. Aim 2: Define the pathogenesis of combinatorial dosage imbalance of 7q genes in JMML.
- Performance Period: 9/20/18-8/31/2023
- Effort: 0.24 CM (2%)
- Contracting/Grants Officer: Chamelli Jhappan
    - Contact Information: Email: jhappanc@mail.nih.gov Phone:

Overlap with the Proposed Project: None

SUBMITTED/PENDING
None

W81XWH2010556: Preventing Blood Cancers and Other Malignancies in Military Personnel at Risk Due to Occupational Radiation Exposure

PI: Stephen Kron, U. of Chicago, IL
Budget: $1,608,718.00
Topic Area: Blood Cancers
Mechanism: FY19 PRCRP Impact Award

Research Area(s): 0200, Genetics and Molecular Biology, 0600, Primary Prevention, 0800 Clinical and Experimental Therapeutics

Award Status: 01-JUL-2020 to 30-JUN-2023

Study Goals:

The primary objective of this study is to evaluate whether increasing protein O-GlcNAcylation can protect and/or mitigate late effects of radiation including bone marrow failure and myeloid neoplasms, using mouse bone marrow culture and wildtype and leukemia-prone mice treated with radiation as models. By validating N-acetyl glucosamine as a radioprotector and radiation countermeasure, we will be poised to translate these findings to protect military and other personnel from the acute and delayed effects of accidental, occupational or military radiation exposures.

Specific Aims:

Aim 1 Examine impacts of hexosamine biosynthetic pathway modulation on repair of double strand breaks, survival, proliferation, senescence and differentiation in bone marrow cultures.
Aim 2 Examine effects of modulation of the hexosamine biosynthetic pathway on repair of double strand breaks and bone marrow integrity and function after total body irradiation.
Aim 3 Examine whether modulation of the hexosamine biosynthetic pathway can alter kinetics of bone marrow failure and myeloid neoplasms in Cux1 knockdown mice.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date

Funding Obtained: none to date